Published in final edited form as:
Exp Biol Med (Maywood). 2010 August ; 235(8): 921–927. doi:10.1258/ebm.2010.010061.

Vitamin D and host resistance to infection? Putting the cart in front of the horse

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Abstract

Vitamin D is being touted as an anti-infective agent and it has even been suggested that vitamin D supplementation could be effective against the H1N1 influenza virus. The claims are largely based on the ability of vitamin D to induce antibacterial peptides and evidence that the immune system produces active vitamin D ($1,25(OH)_2D_3$) *in situ*. While there are many examples of immune production of $1,25(OH)_2D_3$ *in vitro*, there is little *in vivo* evidence. In addition, it is not clear what role immune production of $1,25(OH)_2D_3$ has on the course of disease. Vitamin D and $1,25(OH)_2D_3$ inhibit T helper type 1 (Th1)/Th17-mediated immune responses and autoimmune diseases by acting on the innate and acquired immune system to inhibit the function of Th1 and Th17 cells. Th1 and Th17 cells are important in host resistance to many infections including tuberculosis (TB) caused by *Mycobacterium tuberculosis*. Paradoxically the innate immune system is induced to produce antibacterial peptides that are effective against TB *in vitro*. Data from several models of infection have so far not supported a role for vitamin D in affecting the course of disease. There is also very little evidence that vitamin D affects the course of human TB infection. Experiments have not been done in cells, mice or humans to evaluate the effect of vitamin D on influenza virus. At this time it would be premature to claim that vitamin D has an effect on TB, influenza or any other infection.

Keywords

vitamin D; immunity; infection

Introduction

Recently, there has been a great deal of interest in the role that vitamin D might play in host resistance to infection. The increase in attention came largely as a result of reports of two findings: (1) the immune system could produce the enzyme that converts circulating vitamin D to active vitamin D, and (2) active vitamin D produced in the immune system led to the induction of cathelicidin, which in turn inhibited replication of *Mycobacterium tuberculosis in vitro*.[1] This finding has then led to a number of claims being reported in the scientific and non-scientific communities that claim vitamin D as a broadly anti-infective agent. Two recent letters to the editor suggest that vitamin D supplementation would be beneficial in people infected with influenza.[2,3] In fact, the title of one of them is ‘Pandemic influenza A

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Author contributions: All authors participated in the design, interpretation and writing of the review. We thank Dr Avery August and the members of the Center for Immunology and Infectious Diseases for lively discussions.

(H1N1): Mandatory vitamin D supplementation?'[3] Here we will review the evidence behind the claims that vitamin D status could affect the course of infection. We will first look at the evidence that *in vivo* the immune system produces the vitamin D 1*α*-hydroxylase, then briefly discuss the described roles of vitamin D in the control of innate and adaptive T-cell immunity and then end with a look at the evidence that vitamin D affects *in vitro* and *in vivo* clearance of selected infections, including *M. tuberculosis* and influenza. We conclude that at present the evidence does not support a positive or negative role for vitamin D in host resistance to infection.

Extra-renal production of the vitamin D 1*α*-hydroxylase

In 1970 Fraser and Kodicek[4] first described the kidney as the source of the vitamin D 1*α*-hydroxylase enzyme (*Cyp27B1* gene). The data demonstrated that intact chickens produced but nephrectomized chickens failed to produce what was determined to be $1,25(OH)_2D_3$.[4] Later it was shown by two different groups that patients with advanced renal failure or nephrectomy (prior to transplantation) had no detectable $1,25(OH)_2D_3$ in the blood.[5,6] Experiments in rats using radiolabeled $25(OH)D_3$ (to increase the sensitivity of the assay) showed that normal, otherwise healthy nephrectomized rats failed to produce $1,25(OH)_2D_3$ in the blood, bone or intestine.[7-9] The exception was found in nephrectomized pregnant female rats where extra-renal production of $1,25(OH)_2D_3$ was detected in the blood.[7] More recently, transgenic mice that express the bacterial *LacZ* reporter gene in the place of the vitamin D 1*α*-hydroxylase confirmed the renal-only expression.[10] No reporter gene activity was detected in skin, lung, intestine, skeletal muscle, liver and ovary.[10] Consistent with the earlier finding in rats, expression was found in the placenta of pregnant females.[10] Conversely, measurements by several groups done by mRNA expression and polyclonal antibody staining of tissues have shown 1*α*-hydroxylase expression in healthy tissues including the skin, lymph node and colon of both humans and mice.[11-14] Unlike conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$, these techniques fail to measure enzymatic activity, which is the most reliable measure of the vitamin D 1*α*-hydroxylase enzyme. Therefore, we conclude that under normal physiological conditions, animals and humans (with the exception of pregnant females) express the vitamin D 1*α*-hydroxylase only in the kidneys.

The question of whether extra-renal production of the 1*α*-hydroxylase occurs during disease, however, is still open. Several different reports suggest that during granulomatous diseases in humans, hypercalcemia can exist and may be a result of extra-renal production of $1,25(OH)_2D_3$.[11,15-17] The most convincing example of extra-renal production of the 1*α*-hydroxylase is a single anephric patient with sarcoidosis that had hypercalcemia.[15] The source of the $1,25(OH)_2D_3$ production was linked to lung macrophages isolated from several sarcoidosis patients with hypercalcemia.[18,19] It was also shown that macrophages from other lung diseases did not produce 1*α*-hydroxylase activity.[20] A number of research groups have reported 1*α*-hydroxylase activity *in vitro* from cultured cells. Data from some of these *in vitro* systems have shown that $25(OH)D_3$ is converted *in vitro* to $1,25(OH)_2D_3$ by monocytes and dendritic cells (DCs).[12,21] In particular, human macrophages have been shown to produce the 1*α*-hydroxylase when infected with *M. tuberculosis* and stimulated through toll-like receptors (TLRs[1]). However, there are no credible examples of 1*α*-hydroxylase production *in vivo* from experimental animals. There are reports in mice with experimental colitis that 1*α*-hydroxylase is induced, but the experiment was done using the same polyclonal antiserum that stained a variety of tissues from normal mice and humans described above.[13] The lack of confirmatory data *in vivo* in experimental animals may be due to differences between humans and rodents, lack of vigorous investigation in animals, or perhaps a lack of understanding of the conditions under which the 1*α*-hydroxylase is induced in the immune system *in vivo*.

Reports of extra-renal production of the 1*α*-hydroxylase in the immune system have led investigators to propose a role for this enzyme *in situ* as a source of 1,25(OH)$_2$D$_3$ for use by the immune system.[22] However, in sarcoidosis and other granulomatous diseases the more severe disease phenotypes were associated with increased levels of 1,25(OH)$_2$D$_3$ in the serum, and resolution of the disease following immunosuppressive therapy resulted in the correction of 1,25(OH)$_2$D$_3$ and calcium concentrations.[16,17,23] The autocrine production of 1,25(OH)$_2$D$_3$ may not be beneficial; instead, it might be that immune production of 1,25(OH)$_2$D$_3$ is part of the pathogenic process in granulomatous diseases. More information is needed to determine under what conditions the 1*α*-hydroxylase enzyme is expressed in extra-renal tissues *in vivo* and whether or not expression of this enzyme is a positive or negative contributor to granulomatous diseases in humans.

1,25(OH)$_2$D$_3$ suppresses Th1/Th17-mediated immunity

T helper type 1 (Th1) immune responses are critical for the clearance of many bacterial, viral and parasitic pathogens and autoimmunity can occur when those responses go uncontrolled. Th1 immune responses are characterized by increased interferon (IFN)-*γ* and reduced interleukin (IL)-4. Vitamin D has been shown by several investigators using many different systems to suppress the generation of a Th1 response both *in vitro* and *in vivo*.[24-28] 1,25(OH)$_2$D$_3$ acts directly on T-cells to inhibit T-cell proliferation and IFN-*γ* production.[29,30] In addition to the direct effects of 1,25(OH)$_2$D$_3$ on T-cells, indirect effects of 1,25(OH)$_2$D$_3$ acting on the antigen-presenting cells (APC) also results in decreased Th1 responses.[29] 1,25(OH)$_2$D$_3$ has been recognized as an immuno-suppressive agent that ameliorates the pathogenesis of several different experimental models of Th1 autoimmune diseases, including inflammatory bowel disease (IBD), diabetes, multiple sclerosis (MS), arthritis and several others (reviewed in ref.[24]). Furthermore, vitamin D deficiency and vitamin D receptor (VDR) deficiency in mice have been shown to exacerbate experimental IBD, MS, and diabetes (reviewed in ref.[24])

More recently, in addition to Th1 cells, many of the auto-immune disease models have been shown to depend in part on Th17 cells, which make IL-17. There are reports that treatment of naïve CD4 T-cells during Th17 priming with 1,25(OH)$_2$D$_3$ inhibits IL-17 production.[31] In addition, 1,25(OH)$_2$D$_3$ indirectly suppressed Th17 cell induction by inhibiting DC production of IL-6 and IL-23 that induce Th17 cells.[32] *In vivo*, oral 1,25(OH)$_2$D$_3$ treatment reversed Th17-mediated experimental autoimmune uveitis in mice.[31] The evidence from multiple investigators using several different *in vitro* and *in vivo* systems supports both direct and indirect effects of vitamin D that inhibit Th1 and Th17 responses.

Regulatory T-cell populations require vitamin D

Vitamin D and 1,25(OH)$_2$D$_3$ are required for the optimal development and function of several regulatory T-cells. Regulatory CD4/CD25 + FoxP3 + T (reg) cells are responsible for suppressing immune responses and limiting tissue damage and inflammation. Several groups have shown that while expression of the VDR is not required for development of T regs, 1,25(OH)$_2$D$_3$ increases both number and function of T reg cells.[33,34] 1,25(OH)$_2$D$_3$ has direct effects on the T reg cells and indirect effects via the induction of tolerogenic DCs that promote T reg function to alleviate autoimmune disease.[33] In the gut specialized regulatory T-cells that express the CD8*αα* homodimer protect the gastrointestinal tract from bacterial microflora and other antigens found there. VDR knockout (KO) mice have reduced numbers of CD8*αα* T-cells and are more susceptible to several different models of experimental IBD.[34] Vitamin D is required for the development of CD8*αα* T-cells, and in the gut reduced IL-10 production by the CD8*αα* T-cells is associated with increased experimental IBD in the VDR KO mice.[34] Invariant natural killer T (iNKT) cells are T-cells that can act as regulatory cells and bridge innate and adaptive immunity. Induction of iNKT cells has been shown to be protective in several autoimmune diseases including experimental IBD and MS. Vitamin D regulates iNKT cell development and function and 1,25(OH)$_2$D$_3$ treatment induces cytokine production in iNKT cells.[35] Vitamin D is a positive regulator of several regulatory T-cells and the induction of regulatory T-cells is associated with the beneficial effects of 1,25(OH)$_2$D$_3$ as an inhibitor of Th1/Th17-mediated autoimmunity.

Effect of vitamin D on Th2 immune responses

Th2-mediated immune responses are also regulated by vitamin D. Two studies showed that 1,25(OH)$_2$D$_3$ increased the production of IL-4 and IL-10 by CD4+ T-cells under Th2 cell culture conditions *in vitro*.[36,37] Conversely, it has also been reported that addition of 1,25(OH)$_2$D$_3$ inhibits the production of IL-4 in Th2 cells and does not affect the expression of genes important in Th2 differentiation.[38] *In vivo* experiments in the Th2-mediated disease experimental allergic asthma also provide conflicting results. Using the ovalbumin/alum model of experimental allergic asthma, 1,25(OH)$_2$D$_3$ has been shown to inhibit, induce or to have no effect on symptoms of experimental asthma.[39-41] VDR KO mice failed to develop allergic asthma, while vitamin D deficiency had no effect in the same model.[40] Th2 cells and IL-4 production are inhibited by T reg and Th1 cells, so perhaps the disparate results reflect indirect regulation of Th2 cells via effects on other cell types. The conflicting results on the effects of vitamin D on Th2 cells *in vitro* and in experimental asthma suggest a complicated and as yet not well understood effect of vitamin D on the Th2 cell responses.

Vitamin D and innate immunity

The innate immune system plays an important role in early defense and antigen presentation. Regulation of macrophage and DC function by 1,25(OH)$_2$D$_3$ is important for the inhibition of experimental autoimmunity. 1,25(OH)$_2$D$_3$ treatment of DCs *in vitro* inhibited differentiation and maturation of DC and resulted in DCs that when transferred, induced *in vivo* suppression of alloreactive T-cells.[42] 1,25(OH)$_2$D$_3$-treated DCs produced lower levels of IL-12, and expressed less co-stimulatory and MHC class II molecules than control-treated DCs.[33] Conversely, 1,25(OH)$_2$D$_3$- and lipopolysacharide (LPS)-treated DCs secreted increased amounts of IL-10, and were capable of inducing T reg cell development.[33] The dextran sodium sulfate (DSS) model of acute colitis does not require T-cells and is mediated by the innate immune system. 1,25(OH)$_2$D$_3$ treatment suppressed secretion of several macrophage and DC products *in vitro* (tumor necrosis factor [TNF]-α, IL-1β and IL-6) and experimental DSS induced colitis *in vivo*.[24,32,33,43] VDR KO mice overproduced TNF-α, IL-1β and IL-12 and as a result were extremely susceptible to DSS colitis.[43,44] Vitamin D inhibits DC and macrophage functions such that IL-12-mediated responses are reduced and IL-10-mediated responses are bolstered. In addition, 1,25(OH)$_2$D$_3$ treatment of APC results in the reduced induction of Th1-mediated immune responses while maintaining the ability to induce T regs.

Vitamin D has been shown to regulate TLR-mediated events in multiple cell types. TLR-mediated production of IL-12 and TNF-α was inhibited by 1,25(OH)$_2$D$_3$.[45,46] In neutrophils, 1,25(OH)$_2$D$_3$ suppressed the ability of LPS to induce IL-1β expression as well as inhibited some antimicrobial genes.[47] More recently, 1,25(OH)$_2$D$_3$ has been shown to induce the expression of antimicrobial peptides (cathelicidin and β-defensin) in innate immune cells stimulated through TLR receptors, including monocytes, neutrophils and keratinocytes.[48] Furthermore, 1,25(OH)$_2$D$_3$ treatment enhanced the phagocytosis of monocytes and induced autophagy in macrophages.[48] Stimulation through TLRs in the presence of vitamin D inhibits inflammatory cytokine production (IL-12, TNF-α and IL-1β) in cells of the innate immune system while enhancing several antimicrobial pathways.

Evidence for a role of vitamin D in infectious immunity

Our current understanding of the effects of vitamin D on immune function can be used to predict the effects of vitamin D on host immunity to infectious organisms. The same Th1/ Th17 immune responses that are pathogenic in autoimmunity are protective during infections. In addition, regulatory T-cells not only suppress autoimmune diseases, but also suppress clearance of infectious organisms. Based on the ability of vitamin D to suppress innate and acquired immune responses that result in the suppression of Th1- and Th17-mediated immune responses, we would predict that vitamin D would impair the ability of the host to clear infections dependent on these cell types. Furthermore, vitamin D would be predicted to increase T reg cells that would suppress responses to infectious organisms. However, the ability of vitamin D to induce antibacterial peptides suggests a less straightforward outcome of changes in vitamin D *in vivo* and resultant effects on host resistance to infection.

The experimental data that has looked at the relationship between vitamin D and infections has been summarized in Table 1. *Listeria monocytogenes* is a food-borne pathogen that has commonly been used to study the Th1-mediated immune response to intracellular bacterial infections. Helming *et al*.[49] showed that treating IFN-*γ*-activated macrophages with 1,25(OH)$_2$D$_3$ inhibits listeriacidal activity and suppressed oxidative burst. *In vitro*, VDR KO macrophages were as good as wild-type (WT) for killing *Listeria*.[49] *In vivo*, VDR KO mice produced more IFN-*γ* but showed slightly delayed kinetics in *Listeria* clearance compared with WT.[50] However, VDR KO mice were able to clear *Listeria* infections.[50] 1,25(OH)$_2$D$_3$ treatment of WT mice had no effect on the rate of *Listeria* clearance *in vivo* (unpublished data). Clearance of *Leishmania major* is also dependent on Th1-mediated responses and 1,25(OH)$_2$D$_3$-treated macrophages produced less nitric oxide and killed fewer parasites.[51] Infection of VDR KO mice with *L. major* showed normal Th1 responses and clearance of the organisms.[51] Vitamin D-deficient mice were more susceptible to *Mycobacterium bovis* infection than vitamin D-sufficient mice.[52] The increased susceptibility of vitamin D-deficient mice to *M. bovis* infection was linked to an effect on nitric oxide production.[52] 1,25(OH)$_2$D$_3$ treatment did not alter the ability of mice to clear two infections that require Th1/Th17-mediated immunity (*Candida albicans* or herpes simplex virus-1[53]). Host resistance to *Shistosoma mansoni* requires a strong Th2-mediated response. VDR KO mice had larger liver granulomas (Th2-mediated), but were no different from wild-type mice in their ability to clear a *S. mansoni* infection.[54] In addition, 1,25(OH)$_2$D$_3$ treatment had no effect on the *S. mansoni* infection (unpublished data). Host immunity to *Bordetella pertusis* infection requires Th1 and Th2 responses and VDR KO mice were no different than WT mice in their ability to clear *B. pertusis* infection (unpublished data). The evidence in mice does not support either a beneficial or harmful effect of vitamin D on host immunity to infections that require either Th1/Th17- or Th2-mediated immune responses for clearance.

Vitamin D, tuberculosis and influenza

Vitamin D and 1,25(OH)$_2$D$_3$ induce antibacterial peptides *in vitro* that effectively inhibit tuberculosis (TB). Early studies in 1985 showed that 1,25(OH)$_2$D$_3$ treatment of murine and human macrophages could potentiate the effects of IFN-*γ* to inhibit TB *in vitro*.[55,56] Since 1,25(OH)$_2$D$_3$ treatment suppressed IFN-*γ* production, it remains unclear as to what the effect of 1,25(OH)$_2$D$_3$ would be when additional IFN-*γ* was not added. In mixed cultures of cells from TB patients, 1,25(OH)$_2$D$_3$ reduced the production of IFN-*γ* and TNF-*α*.[57] Inhibition of IFN-*γ*, IL-12 and TNF-*α* by a variety of means are associated with an increased risk to TB infection.[58-62] Unfortunately, there are no experiments that have looked at both the IL-12/ IFN-*γ*-inhibiting and cathelicidin-inducing effects of 1,25(OH)$_2$D$_3$ on macrophages. Without a better understanding of the relationship between the antibacterial and IL-12 suppressive responses, it is difficult to predict what the net effect of vitamin D would be on host resistance to TB.

Epidemiological data suggest that low vitamin D status is associated with TB severity or susceptibility.[63] Often mentioned is the anecdotal association that patients placed in the sun would see improvement in TB symptoms. A meta-analysis showed a positive association between VDR polymorphisms and host susceptibility to TB.[63] Recently, a double-blind, randomized and placebo-controlled trial used three high dose (100,000 IU) vitamin D supplements in TB patients.[64] The study showed no beneficial effect in clinical outcome or mortality in TB.[64] Another recent report in dialysis patients showed no correlation between vitamin D supplementation and decreased risk of TB infection.[65] Thus far, the evidence in humans with TB does not support a beneficial or harmful role of vitamin D supplementation.

It is estimated that at least one upper respiratory tract infection (URI) afflicts 72% of adults each year.[66] The effect of vitamin D on URI is based on epidemiological data and therefore associations. 25(OH)D_3 levels have been inversely associated with URI incidence.[66] In a randomized, double-blind trial of vitamin D supplementation, vitamin D was shown to have no effect on the clinical course of URIs.[67] In 2006 Cannell *et al*.[68] suggested that children who received vitamin D supplements had a decreased incidence of respiratory infections and attributed this observation to vitamin D regulation of the antimicrobial peptides cathelicidin and defensin β2. Vitamin D has been shown to increase the expression of antibacterial peptides; however, the effect of vitamin D on these antibacterial peptides *in vitro* or *in vivo* against influenza has not been tested. Leikina *et al*.[69] showed that retrocyclin (not shown to be a vitamin D target), a theta-defensin (that is not expressed by humans), can inhibit influenza virus in a canine-derived cell line. Any effect of either vitamin D or 1,25$(OH)_2D_3$ on influenza replication *in vitro* and/or *in vivo* has so far not been tested.

Conclusions

At present, there is not adequate information available to claim vitamin D as an anti-infective agent. The data supporting vitamin D as a factor that could improve resistance to infection are based on *in vitro* experiments that demonstrate immune cells make the vitamin D 1α-hydroxylase, and that 1,25$(OH)_2D_3$ induces antibacterial peptides that kill TB. However, contradictory data exist that host immune responses important in the control of TB are inhibited by vitamin D and 1,25$(OH)_2D_3$. Furthermore, it is unclear as to whether immune-mediated production of 1,25$(OH)_2D_3$ is protective or pathogenic. *In vivo* experiments to address the signals and role of immune produced 1,25$(OH)_2D_3$ have not been done. In experimental animals the data neither support nor refute an effect of vitamin D on several infections. Data from humans show associations between vitamin D status or genetic polymorphisms and TB. There are no data to support any relationship between vitamin D and host resistance to influenza. At this time it would be premature to suggest that vitamin D might be useful to improve host resistance to TB, influenza or any other infectious organism.

Acknowledgments

This work was supported by National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases DK070781 and National Center for Complementary and Alternative Medicine and the Office of Dietary Supplements AT005378 to MTC.

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Table 1

Effect of vitamin D on experimental infection rate

Pathogen	Immune response*	Vitamin D status†	Infection rate‡	Reference
Listeria monocytogenes	Th1	D–	NE, ↑	49,50
Listeria monocytogenes	Th1	1,25D3	NE, ↑	49,50
Leishmania major	Th1	D–	NE	51
Leishmania major	Th1	1,25D3	↑	51
Mycobacterium bovis	Th1	D–	↑	52
Mycobacterium tuberculosis	Th1	1,25D3	↓	1
Candida albicans	Th1/Th17	1,25D3	NE	53
Herpes simplex	Th1/Th17	1,25D3	NE	53
Shistosoma mansoni	Th2	D–	NE	54
Shistosoma mansoni	Th2	1,25D3	NE	Unpublished
Bordetella pertusis	Th1/Th2	D–	NE	Unpublished

Th, T-helper cells

*Protective T-cell response against the pathogen

†D–: Experiments performed in vitamin D-deficient or VDR KO mice; 1,25D3: Experiments performed in vitamin D-sufficient or 1,25(OH)$_2$D$_3$ supplemented cells or mice

‡Decreased infection: ↓; increased infection: ↑; no effect: NE